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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,420	11/26/2003	Stanley Beames Brown	0001530USQ/3049	2642

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,420	BROWN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-53 and 65-97* is/are pending in the application.

4a) Of the above claim(s) *44-53,65-76,80-83,85-88,92,94,96-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-79,84,89-91,93 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *26 November 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 44-53 and 65-97 are presented for examination.

Acknowledgement is made of the present application as a continuation-in-part (CIP) of PCT Application No. PCT/GB02/02278, filed May 30, 2002, which also claims priority under 35 U.S.C. 119(a-d) to United Kingdom Patent Application Nos. 0113121.8, filed May 30, 2001 and 0123945.8, filed October 5, 2001. Applicant's Information Disclosure Statement (IDS) filed November 26, 2003 has been received and entered into the application. As reflected by the attached, completed copy of form PTO-1449 (one page total), the Examiner has considered the cited reference.

Requirement for Restriction/Election

Restriction between the plurality of inventions contained within the present claims was required under 35 U.S.C. 121. Applicant was required to elect one of the inventions from any one of Groups I-V and one single disclosed species of phenothiazinium compound in the requirement for restriction/election dated April 11, 2005. Applicant's response to such a requirement filed June 13, 2005 cancelled all of originally presented claims 1-43 and added new claims 44-86.

The previous requirement for restriction/election dated April 11, 2005 was rendered **moot** due to the cancellation of all of the originally presented claims. Applicant was required to elect one of the inventions from any one of Groups I-V and one single disclosed species of phenothiazinium compound in the requirement for restriction/election dated July 1, 2005 based

on newly added claims 44-86. Applicant's response to such a requirement filed September 1, 2005 cancelled claims 54-64 and added newly claims 87-97 in lieu thereof.

Due to the fact that the elected group of claims in the response to restriction/election filed September 1, 2005 was also drawn to a plurality of patentably distinct inventions, the previous requirement for restriction/election was **vacated** in place of the requirement dated October 27, 2005, based on currently pending claims 44-53 and 65-97.

Applicant's election **with traverse** of the invention of Group VII (claims 77-79. 84, 89-91, 93 and 95), drawn to methods of treating microbial infections, burn wounds, dental bacterial disease or antibiotic resistant bacteria, or sterilization of a surface or fluid comprising the administration or application of a compound of formula (I), and the election of the tetra-butyl compound 3,7-(tetra-n-butylamino)-phenothiazin-5-ium bromide as the single disclosed species of phenothiazinium compound of formula (I) [where A and B are both (-NR1R2), R1 and R2 are both n-butyl, P=1 and Xp- is bromide], in the reply filed November 28, 2005 is acknowledged. Applicant's traversal is on the grounds that all of the groups are classed and subclassed identically and, thus, no undue burden would be placed on the Examiner to search all of the groups if they were considered together.

Applicant's traversal has been carefully considered. However, while it may be true that the groups are classed and subclassed identically, it remains that Invention I and Inventions II-VIII are independent and patentably distinct because the compounds of Invention I are known to be used for a variety of materially different uses, each which require distinctly different process steps in distinctly different populations of subjects with distinctly different outcomes. Thus, regardless of the classification, a search for the subject matter of Invention I would not

necessarily encompass a comprehensive search for the subject matter of any one of Inventions II through VIII.

Furthermore, the methods of each of Inventions II-VIII each have a separate and distinct outcome from the expected outcome of any one or more of the other inventions. Each of the methods would be practiced in distinctly different populations of subjects, such that the dosage amounts required to attain the therapeutic objective of the method would be distinctly different for each one of the methods. While there may be incidental overlap in the groups of patients experiencing, for example, arteriosclerosis, and those experiencing, for example, cancer, the therapeutic objectives, endpoints, steps and dosages required to treat such dissimilar conditions are vastly different and do not reasonably anticipate, suggest or render obvious the treatment of any one of the other conditions.

The distinct nature of the Inventions of Groups II-VIII is further supported by the fact that each disease has a different and distinct etiology and pathophysiological manifestations, and that each is differently treated. Such is sufficient to indicate that each of the methods of treating the presently claimed disease states is differently searched in the patent and non-patent literature and that a search for one disease will not necessarily result in a comprehensive search of any one or more of the other diseases listed. As a result, an undue burden would be placed on the Examiner to search each of Applicant's presently claimed methods. Notwithstanding that Applicant may have established an underlying commonality for the claimed diseases, it remains that each of the diseases are recognized in the art as being clinically and pathophysiologically distinct from one another and, thus, each of the above-identified groups is fully capable of supporting separate patents.

Consideration of the plurality of inventions that Applicant has claimed would significantly compromise and preclude a quality examination on the merits. Furthermore, execution of a search encompassing the entirety of Applicant's compounds and multiple therapeutic objectives would not only constitute an undue burden on the Examiner, but *consideration of the findings* of such a search in accordance with the requirements of the law under 35 U.S.C. §§101, 102, 103 and 112 would be unduly onerous.

Moreover, it is further noted that a comprehensive search for the presently claimed subject matter is not solely limited to a search of the class and subclass in which it is classified. Therefore, it is obvious that a comprehensive search of the copious amounts of patent and non-patent literature for each of the eight patentably distinct inventions presently claimed would necessarily place an undue burden on the Examiner.

Therefore, for the reasons above and those made of record at pages 2-10 of the previous Office Action dated October 27, 2005, the restriction requirement is deemed proper and is made **FINAL**.

Claims 44-53, 65-76, 80-83, 85-88, 92, 94 and 96-97 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being to non-elected inventions, there being no allowable generic or linking claim.

The claims corresponding to the elected subject matter are 77-79, 84, 89-91, 93 and 95 and such claims are herein acted on the merits.

Applicant's Claims for Priority

Acknowledgment is made of Applicant's request to afford the present application (a continuation-in-part of PCT Application No. PCT/GB02/02278) the benefits of the earlier filing date (May 30, 2002). However, the propriety of this priority claim cannot be determined in the absence of a copy of the disclosure of this PCT application. Absent such a copy, it cannot be determined whether the disclosure of this PCT application contains sufficient description and adequate enablement under 35 U.S.C. 112 to support the presently claimed subject matter and to properly grant Applicant the effective filing date of May 30, 2002.

Acknowledgment is further made of Applicant's request to afford the present application the benefit of the earlier filing dates of United Kingdom Patent Application 0113121.8, filed May 30, 2001, or United Kingdom Patent Application 0123945.8, filed October 5, 2001, under 35 U.S.C. 119(a-d).

It is noted, however, that Applicant has not filed a certified copy of United Kingdom Patent Applications 0113121.8 or 0123945.8 as required by 35 U.S.C. 119(b).

As a result, the priority claim of the present application cannot be determined. It is unclear how much of the presently claimed subject matter is supported by PCT/GB02/02278 since a copy of the disclosure of said PCT has not been furnished to the Office. Furthermore, in the absence of any certified copies of either United Kingdom patent applications, Applicant's claims for foreign priority under 35 U.S.C. 119(a-d) cannot be granted because the requirements have not been met.

Accordingly, the effective filing date of the present application is **November 26, 2003**.

Search and Examination of the Presently Elected Compound

Examination of the present claims was performed herein to the extent that the elected method(s) reads upon the use of the compound 3,7-(tetra-n-butylamino)-phenothiazin-5-ium bromide. A search by the Examiner determined that the use of such a compound for treating microbial infections, burn wounds, dental bacterial disease or antibiotic resistant bacteria, or sterilization of a surface or fluid was not taught or suggested by the prior art.

Examination of the present claims is further expanded to the extent that the elected method reads upon the use of a compound of formula (I), wherein R' and R'' read upon any optionally substituted linear, branched or cyclic hydrocarbon group other than n-butyl or R^{3} and R'' together with the N atom to which they are attached form an optionally substituted 5-, 6- or 7-membered ring.

Objection to the Specification

Applicant requested an amendment to the specification to add continuity and priority claims in the transmittal letter dated November 26, 2003 under Part (4). However, Applicant has improperly identified the PCT Application to which the present application claims priority as PCT/GB03/02278, instead of PCT/GB02/02278. Applicant may wish to consider amending the first line of the specification in the following manner. It is noted that the acceptance of such a suggestion does not necessarily equate to the present claims being free of any cited prior art.

---This is a continuation-in-part of application serial no. ~~PCT/GB03/02278~~ PCT/GB02/02278, filed May 30, 2002, which claims priority from Great Britain application

Serial no. 0113121.8 filed on May 30, 2001 and Great Britain application Serial No. 0123945.8 filed October 5, 2001.---

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-79, 84, 89-91, 93 and 95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The presently claimed and elected invention is drawn to the use of a compound of formula (I) for the treatment of microbial infections, burn wounds, dental bacterial disease or antibiotic resistant bacteria, or the sterilization of a surface or fluid. Applicant has intended the following proviso to exclude "the compounds in which A and B are both either –N(CH3)2 or –N(CH2CH3)2" as recited in, for example, claim 77. However, while such a proviso has been noted, it is not clear as to exactly which compounds Applicant is intending to exclude from the presently claimed invention.

In particular, the use of the phrase "the compounds in which A and B are both either" does not adequately convey the subject matter that Applicant intends to be excluded from the scope of the invention. For example, such a proviso may be interpreted to mean that compounds in which A and B are both –N(CH3)2 ***or*** compounds in which A and B are both –N(CH2CH3)2 are excluded from the presently claimed invention. However, an equally reasonable reading of such a proviso may be interpreted to mean that compounds in which A is –N(CH3)2 and B is –

N(CH2CH3)2 ***or*** A is –N(CH2CH3)2 and B is –N(CH3)2 are excluded from the presently claimed invention. Thus, there are, at minimum, four different interpretations of the compounds Applicant is intending to exclude from the present claims. Such language fails to set forth the presently claimed subject matter with reasonable clarity, deliberateness and precision.

In light of such, and additionally noting that the claims have been read in light of the specification, it remains that the language in the claims does not expressly and specifically set forth that which Applicant regards as the invention and that for which Applicant is seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination and the application of prior art, the claims will be interpreted to read upon the exclusion of compounds in which A is –N(CH3)2 and B is –N(CH2CH3)2 ***or*** A is –N(CH2CH3)2 and B is –N(CH3)2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I Claims 79 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner (WO 91/16911; 1991) in light of *The Merck Index* (Monograph 5979, 1989; cited to show a fact).

In accordance with the MPEP at §2131.01, it is proper to use a secondary reference for a rejection under 35 U.S.C. 102, provided that the reference is relied upon to define a term used in the primary reference.

Wagner teaches a method of decontaminating blood or cellular blood components (considered to meet Applicant's limitation of "sterilizing ... a fluid" as recited in present claim 79 or "sterilization of ... fluids" as recited in present claim 95; see page 6, lines 7-9), comprising the addition of methylene blue (a phenothiazin-5-ium dye; page 6, lines 9-11 and page 8, lines 3-5) in an effective concentration acceptable for transfusion, such that the treated blood or blood component does not require additional manipulation to remove the dye (i.e., the dye remains in the blood or blood component and is, therefore, administered directly to the subject via the blood or blood component; see page 15, lines 4-15), and then treating said blood or blood components with light at an effective wavelength and intensity, wherein the light is absorbed by said dye and results in the inactivation of substantially all pathogenic contaminants (i.e., any virus, bacterium or parasite; see page 10, lines 22-25) in said blood or blood components (considered to meet Applicant's limitation of "activating said compound by means of light" as recited in present claim 79; see page 6, lines 11-25).

The Merck Index (1989) is relied upon to show that the compound methylene blue is of the identical core structure as that presented as Formula (I) in present claim 79, wherein R' and R'' are both methyl substituents, chloride is the counteranion and P=1. Please reference the section "Claim Rejection-35 U.S.C. 112, Second Paragraph" for a discussion of the claim language insofar as it has been interpreted to read upon the exclusion of particular phenothiazinium compounds from the present claims.

II Claims 77, 79, 89-90, 93 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilson et al. (U.S. Patent No. 5,611,793; 1997) in light of *The Merck Index* (Monograph 5979, 1989; cited to show a fact).

In accordance with the MPEP at §2131.01, it is proper to use a secondary reference for a rejection under 35 U.S.C. 102, provided that the reference is relied upon to define a term used in the primary reference.

Wilson et al. teaches a method for disinfecting (considered to meet Applicant's limitation of "treatment of microbial infections" as recited in present claim 77, "treatment of microorganisms" as recited in present claim 89 or "anti-microbial treatment for...other local infections" as recited in present claim 93; see col.1, lines 28-30) or sterilizing tissues or a wound or lesion (considered to meet Applicant's limitation of "sterilizing a surface" as recited in present claim 79 or "sterilization of surfaces" as recited in present claim 95; see col.1, lines 28-30) in the oral cavity of a patient comprising the topical application (considered to meet Applicant's limitation of "by application to the area to be treated" as recited in present claim 77, "contacting or applying" as recited in present claim 79 or "applying to or contacting with" as recited in present claim 95; see col.1, lines 28-34 and col.4, lines 55-65) of a photosensitizing compound (col.1, lines 28-34 and col.2, lines 37-62), such as methylene blue (col.2, line 46; see present claims 77, 79, 89-90, 93 and 95), to the tissues, wound or lesion (considered to meet Applicant's limitation of a "surface" as recited in present claims 79 and 95; see col.1, lines 28-34) and irradiating the tissues, wound or lesion with laser light at a wavelength absorbed by the photosensitizing compound (col.1, lines 28-34; see present claims 77, 79, 89-90, 93 and 95),

wherein the method may be used for the destruction of disease-related microbes related to chronic periodontitis and gingivitis (col.2, lines 1-7), cariogenic microbes on a tooth surface in order to treat or prevent dental caries (col.2, lines 10-11), or treatment of oral candidiasis (col.2, lines 14-16; each considered to meet Applicant's limitation of "treatment of ...dental bacterial disease" as recited in present claim 77 or "anti-microbial treatment ... for the treatment of dental bacterial disease" as recited in present claim 93).

The Merck Index (1989) is relied upon to show that the compound methylene blue is of the identical core structure as that presented as Formula (I) in present claim 79, wherein R' and R'' are both methyl substituents, chloride is the counteranion and P=1. Please reference the section "Claim Rejection-35 U.S.C. 112, Second Paragraph" for a discussion of the claim language insofar as it has been interpreted to read upon the exclusion of particular phenothiazinium compounds from the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I Claims 79, 84 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner (WO 91/16911; 1991) in light of *The Merck Index* (Monograph 5979, 1989; cited to show a fact) in view of Shanbrom (U.S. Patent No. 6,183,764; 2001).

Wagner teaches a method of decontaminating blood or cellular blood components (considered to meet Applicant's limitation of "sterilizing ... a fluid" as recited in present claim 79 or "sterilization of ... fluids" as recited in present claim 95; see page 6, lines 7-9), comprising the addition of methylene blue (a phenothiazin-5-ium dye; page 6, lines 9-11 and page 8, lines 3-5) in an effective concentration acceptable for transfusion, such that the treated blood or blood component does not require additional manipulation to remove the dye (i.e., the dye remains in the blood or blood component and is, therefore, administered directly to the subject via the blood or blood component; see page 15, lines 4-15), and then treating said blood or blood components with light at an effective wavelength and intensity, wherein the light is absorbed by said dye and results in the inactivation of substantially all pathogenic contaminants (i.e., any virus, bacterium or parasite; see page 10, lines 22-25) in said blood or blood components (considered to meet Applicant's limitation of "activating said compound by means of light" as recited in present claim 79; see page 6, lines 11-25).

The Merck Index (1989) is relied upon to show that the compound methylene blue is of the identical core structure as that presented as Formula (I) in present claim 79, wherein R' and R'' are both methyl substituents, chloride is the counteranion and P=1.

The difference between the Wagner reference and the presently claimed subject matter lies in that the reference fails to teach the administration of the phenothiazin-5-ium dye compound in a conjugate or composite formulation with a polymer for the sterilization of fluids (see present claim 84).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because the use of a disinfectant microbicidal dye compound, such as methylene blue, in conjunction with a polymeric material, was well known in the art at the time of the invention.

In this regard, Shanbrom (U.S. Patent No. 6,183,764; 2001) is cited. Shanbrom teaches an organic polymer material to which is tightly adsorbed a disinfectant organic dye (see abstract, lines 1-5), such as methylene blue (col.2, lines 30-40). Shanbrom teaches the exposure of squares of polyvinyl chloride treated with methylene blue and gentian violent to blood or plasma as the microbial growth medium and reported effective microbicidal activity (col.4, lines 8-31). Shanbrom discloses that the unusual effectiveness of the polymer-dye material was most likely due to the adsorption of the dye to the polymer, which prevents it from washing away and becoming too dilute to be effective (col.4, lines 46-49).

In light of such, it would have been *prima facie* obvious to one of ordinary skill in the art to employ a dye compound, such as the methylene blue dye disclosed by Wagner, in conjunction

with a polymeric material for the sterilization of fluids, such as the blood or blood products disclosed in Wagner. Such a person would have been motivated to employ a dye-polymer combination because the teachings of Shanbrom raise the reasonable expectation of success that the use of the disinfectant dye in combination with a polymer would have exerted an increased and prolonged anti-microbial efficacy of the compound because the presence of the polymer would assist in increasing the resident time of the microbicidal dye compound in the fluid (i.e., blood or blood component(s)) by resisting dilution of the dye to the point of inactivating its anti-microbial effect.

II Claims 77, 79, 89-91, 93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al. (U.S. Patent No. 5,611,793; 1997) in light of *The Merck Index* (Monograph 5979, 1989; cited to show a fact) in view of Biel (WO 01/62289; 2001).

Wilson et al. teaches a method for disinfecting (considered to meet Applicant's limitation of "treatment of microbial infections" as recited in present claim 77, "treatment of microorganisms" as recited in present claim 89 or "anti-microbial treatment for...other local infections" as recited in present claim 93; see col.1, lines 28-30) or sterilizing tissues or a wound or lesion (considered to meet Applicant's limitation of "sterilizing a surface" as recited in present claim 79 or "sterilization of surfaces" as recited in present claim 95; see col.1, lines 28-30) in the oral cavity of a patient comprising the topical application (considered to meet Applicant's limitation of "by application to the area to be treated" as recited in present claim 77, "contacting or applying" as recited in present claim 79 or "applying to or contacting with" as recited in present claim 95; see col.1, lines 28-34 and col.4, lines 55-65) of a photosensitizing compound

(col.1, lines 28-34 and col.2, lines 37-62), such as methylene blue (col.2, line 46; see present claims 77, 79, 89-90, 93 and 95), to the tissues, wound or lesion (considered to meet Applicant's limitation of a "surface" as recited in present claims 79 and 95; see col.1, lines 28-34) and irradiating the tissues, wound or lesion with laser light at a wavelength absorbed by the photosensitizing compound (col.1, lines 28-34; see present claims 77, 79, 89-90, 93 and 95), wherein the method may be used for the destruction of disease-related microbes related to chronic periodontitis and gingivitis (col.2, lines 1-7), cariogenic microbes on a tooth surface in order to treat or prevent dental caries (col.2, lines 10-11), or treatment of oral candidiasis (col.2, lines 14-16; each considered to meet Applicant's limitation of "treatment of ...dental bacterial disease" as recited in present claim 77 or "anti-microbial treatment ... for the treatment of dental bacterial disease" as recited in present claim 93).

The Merck Index (1989) is relied upon to show that the compound methylene blue is of the identical core structure as that presented as Formula (I) in present claim 79, wherein R' and R'' are both methyl substituents, chloride is the counteranion and P=1.

The differences between the Wilson reference and the presently claimed subject matter lie in that the reference fails to teach:

(i) the treatment of antibiotic resistant bacteria (see present claim 91); or

(ii) systemic administration of the active dye compound (see present claim 77).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i and ii) Disinfection and sterilization of the oral cavity insofar as the infected tissue, wound or lesion in the oral cavity resulted from antibiotic resistant bacteria would have been *prima facie* obvious to one of ordinary skill in the art.

In this regard, Biel (WO 01/62289; 2001) is cited. Biel teaches that methylene blue based photodynamic therapy has been demonstrated in vitro and in vivo to be effective in the photoeradication of antibiotic resistant gram positive and gram negative bacteria. Biel further teaches that methylene blue has very low tissue toxicity and can be administered to humans orally and intravenously in high doses without any toxic effects (see paragraph bridging pages 6-7).

In light of such, it would have been *prima facie* obvious to the skilled artisan to employ the photosensitizing compound, methylene blue, in combination with laser light to treat infections of the oral cavity and oral surfaces as they result from antibiotic resistant bacteria. Such a person would have been motivated to do so since it was well known in the art at the time of the invention that such a photosensitizing dye (i.e., methylene blue) demonstrated significant microbicidal efficacy, both in vitro and in vivo, in eradicating antibiotic resistant gram positive and gram negative bacteria. Thus, the therapy containing methylene blue as the active disinfectant compound disclosed by Wilson et al. would also have been reasonably expected to exert similar efficacy against antibiotic resistant bacteria.

Moreover, it is noted that Biel also teaches the compatibility of methylene blue with oral and intravenous administration (see paragraph bridging pages 6-7). Thus, while Wilson et al. expressly teaches the topical administration of the disclosed photosensitizing composition, it would have been *prima facie* obvious to one of ordinary skill in the art to adapt the therapy for

both oral or intravenous administration (i.e., systemic) of the photosensitizing dye compound, since it was well known in the art that such a compound was amenable to such formulations and would not exert undue toxicity on surrounding tissues or the subject as a whole. Such a determination would have been made in accordance with a variety of factors, including, but not limited to, the dosage amount to be administered, the frequency and ease of administration, the site to be treated, the severity of disease, and patient compliance with the regimen. In the absence of evidence to the contrary, the currently claimed routes of administration are not seen to be inconsistent with those that would have been determined by the skilled artisan. Furthermore, it is noted that the skilled artisan would have reasonably expected to retain the microbicidal activity of the composition, regardless of the formulation (i.e., topical or systemic), absent any factual evidence or direction to the contrary.

III Claims 77 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biel (WO 01/62289; 2001) in view of *The Merck Index* (Monograph 5979, 1989) and Wainwright et al. ("Photobactericidal Activity of Phenothiazinium Dyes Against Methicillin-Resistant Strains of *Staphylococcus Aureus*", FEMS Microbiology Letters, 160 (1998): 177-181).

Biel teaches a method of treating an infection by identifying the in vivo area of infection, applying or dispensing a concentration including a photosensitive material, such as methylene blue, and a surfactant, to the area of infection and exposing the area of infection with a light having a light wavelength, light dosage and a light dosage rate (see paragraph bridging pages 3-4 and present claims 77 and 93). Biel teaches that methylene blue based photodynamic therapy has been demonstrated in vivo to be effective in the photoeradication of antibiotic resistant gram

positive and gram negative bacteria (see paragraph bridging pages 6-7) and may be administered to the site to be treated via topical application or intravenous or subcutaneous injection (see page 12, lines 5-8 of second full paragraph and present claims 77 and 93).

The Merck Index (1989) is relied upon to show that the compound methylene blue is of the identical core structure as that presented as Formula (I) in present claim 79, wherein R' and R'' are both methyl substituents, chloride is the counteranion and P=1. Please reference the section "Claim Rejection-35 U.S.C. 112, Second Paragraph" for a discussion of the claim language insofar as it has been interpreted to read upon the exclusion of particular phenothiazinium compounds from the present claims.

The differences between the Biel reference and the presently claimed subject matter lie in that the reference fails to teach the particular administration of the photodynamic therapy for the treatment of skin infections or burn wounds (see present claims 77 or 93).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because the art recognized phenothiazinium dyes, such as methylene blue and its derivative compounds, as having photobactericidal activity against methicillin-resistant strains of Staphylococcus aureus.

In this regard, Wainwright et al. ("Photobactericidal Activity of Phenothiazinium Dyes Against Methicillin-Resistant Strains of *Staphylococcus Aureus*", FEMS Microbiology Letters, 160 (1998): 177-181) is cited. Wainwright et al. teaches that illumination of methylene blue led to an increase in bactericidal activity against several pathogenic strains of Staphylococcus

aureus, four of which were methicillin resistant (i.e., antibiotic resistant strains; see abstract at page 177 and Table 2 at page 179). Wainwright et al. further teaches and suggests that staphylococcal infections or colonization found in epidermal wounds or burns may be accessible to topical treatment with such bactericidal agents (see col.1, second paragraph at page 178).

In light of such, the treatment of epidermal wounds (considered to meet Applicant's limitation of "skin infections" as recited in present claims 77 or 93) or burn wounds infected with antibiotic resistant bacteria using methylene blue based photodynamic therapy would have been *prima facie* obvious to one of ordinary skill in the art. Considering the teachings of Biel, who expressly discloses the efficacy of methylene blue photodynamic therapy in the treatment of infections caused by antibiotic resistant bacteria, and further in view of Wainwright et al., who not only confirms the bactericidal activity of methylene blue, but also teaches that such an agent would be amenable to topical application to epidermal wounds or burns infected with antibiotic resistant bacteria, it would have been apparent to the skilled artisan that the methylene blue photodynamic therapy disclosed in Biel would have efficacy in treating such wound types, particularly when infected with antibiotic resistant bacteria. It is noted that the teachings of Wainwright et al. raise the reasonable expectation of success that a photodynamic therapy comprising methylene blue would have efficacy in treating epidermal or burn wounds found to be infected with antibiotic resistant (e.g., methicillin resistant) bacteria.

Conclusion

Rejection of claims 77-79, 84, 89-91, 93 and 95 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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January 5, 2006

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